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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/435,733	11/08/99	GALDES A	CIBT-P02-052

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EXAMINER	
BRANNOCK, M	
ART UNIT	PAPER NUMBER
1646	18

DATE MAILED: 08/15/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
09/435,733	Galdes et al.
Examiner	**Art Unit**
Michael Brannock, Ph.D.	1646

-- Th MAILING DATE of this communication appears on the cover sheet with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-51 is/are pending in the applica

4a) Of the above, claim(s) 12, 24-29, 32-40, 42, 43, and 49 is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-11, 13-23, 30, 31, 41, 44-48, 50, and 51 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4,5

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 17, 5/29/01, have been entered in full.

2. Claims 1-51 are pending.

3. Claims 12, 24-29, 32-40, 42, 43, and 49 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 17. Additionally, claims 1-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50 and 51 will be examined only to the extent that the claims are directed to methods of treatment of diabetic neuropathy comprising the administration of a sonic hedgehog polypeptide, as per Applicants' election in Paper 17. It is noted that claim 49 is included in Group I but does not encompass the elected species, and are therefore withdrawn from consideration.

The traversal is on the grounds that a search of Groups I-VII would not be a serious burden on the examiner. In particular, Applicant points out that the claims of group I are not limited to uses of Sonic hedgehog polypeptide but also include polypeptides with functional homology. Further, Applicant asserts that an examination of group I would necessarily include a search of methods of gene therapy, therapy involving small molecule antagonists, and antisense nucleic acids. This is not found persuasive for the following reasons:

Under MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 8702.01, 806.04, 808.01) **or** distinct as claimed (see MPEP § 806.05- §806.05(I)): and

(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a)- 806.04(I), § 808.01(a), and § 808.02).

Consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together: (C) a different field of search. These criteria were met in the above restriction, as put forth in the previous office action. Further, a search is directed not only to art which would be anticipatory, but also to art that would render the invention obvious. Although a search of any one of the groups may overlap that of another, the search of one group could not be relied upon, solely, to provide art that is anticipatory or would render obvious the invention of any other group, and to search all groups would be burdensome. Therefore, the restriction is maintained and made final.

Additionally, Applicant traverses the species restriction requirement. Applicant asserts that "the claims are already directed to a single patient population, those suffering from a form of neuropathy". This argument has been fully considered but not deemed persuasive because the claims are directed to multiple forms of neuropathy, each being recognized in the art as being distinct (e.g. claim 47), having divergent etiologies, requiring divergent diagnoses and treatments. Therefore, the restriction requirement is maintained and made final.

Specification

4. The disclosure is objected to because of the following informalities:

Page 1, line 13: "the" is garbled.

Page 9, line 29: treatment is misspelled.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 1-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50 and 51 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well established utility.

Claims 1-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50 and 51 require a method of preventing dysfunction and/or degradation of functional performance of motor or sensory nerves. However, the term "preventing", given its broadest reasonable interpretation with the specification, requires that absolutely no cell, nor tissue, would present any symptom of a disorder after treatment with the hedgehog polypeptides. There is no evidence, either in the specification nor in the prior art, that any method to date can accomplish this goal. The specification presents the results of several experiments demonstrating that exogenous application of hedgehog can protect from

damage or accelerate healing of certain neurologic systems, however there is no support for the prevention of any disorder, as is required by the claims, and neither can such support be obtained through reasonable extrapolation of the data.

Claims 26-32 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50 and 51 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons:

The claims require a "hedgehog or ptc therapeutic". The specification defines "ptc therapeutic" as that which mimics the effect of naturally occurring hedgehog proteins on patched signaling (see page 11). The specification further appears to define "ptc therapeutic" as a molecule which "binds to patched and alters its signal transduction activity , or compounds which alter the binding and/or activity of a protein (e.g., intracellular) involved in patched signal

pathway, and compounds which alter the level of expression of a hedgehog protein, a patched protein or a protein involved in the intracellular signal transduction pathway of patched (see page 47, lines 23-28 and claims 30 and 31). Thus, "hedgehog or ptc therapeutic" appears to encompass any and all compounds that alter the activity of patched. However, it is well appreciated that the activities of patched are extremely complex and as yet controversial and incompletely identified (see Stull and Iacovitti, Experimental Neurobiology 169(1)36-43, 2001, especially page 40), therefore the phrase "hedgehog or ptc therapeutic" renders the claims indefinite because those skilled in the art would have to identify the activities of patched in order to determine whether a compound alters these activities.

Further the recitation of the term " hedgehog polypeptide" without reference to a particular amino acid or nucleic acid sequence renders the claims indefinite because the specification has not put forth that material or functional element that is indicative of a "hedgehog polypeptide" and nor is such a definition known in the prior art which clearly sets forth which polypeptides are hedgehog polypeptides and which are not. Therefore the metes and bounds of the claims cannot be determined.

The claims require methods of preventing dysfunction and/or degradation of functional performance of motor or sensory nerves comprising administering a "therapeutic amount" or an "effect amount" of a "ptc therapeutic" or a "therapeutically effective amount" of a "ptc therapeutic", or a "protective amount", yet the claims fail to require that amount be "effect" or "therapeutically effective" at any particular thing or that the amount be protective of any

particular thing. Thus, it is unclear what the "ptc therapeutic" is protective or therapeutically effective for. Therefore, the metes and bounds of the claims cannot be determined.

Claims 7, 8, 10, 11, 13-23, 30, 31, 41, 44, 45-47, 48, 50 and 51 require an amino acid sequence that is homologous to an amino acid sequence. Homology is a relative term and it is used in the art to provide a comparison between two amino acid sequences; yet the term, alone, does not provide a definition of the degree of similarity within the comparison. In the instant case, it is the degree of similarity between the claimed amino acid sequence and the reference sequences that determines the metes and bounds of the claim. As this degree of similarity is not set forth, either in the claims or in the specification, the metes and bounds of the claims cannot be determined.

Claim 10 requires that the nucleic acid hybridize under stringent conditions. The term "stringent conditions" is confusing because it is a relative term and encompasses conditions of varying degrees of stringency - such conditions determining the bounds of the claim. However, the art does not provide an unambiguous definition of the term "stringent conditions" and neither is such a definition given for the term in the specification which puts forth the metes and bounds of the claim Applicant is seeking protection for. It is suggested that the claim recite the actual conditions that applicant considers to be stringent, i.e., salt concentration and temperature conditions of incubations and washes.

In claim 41 the word "patient" lacks antecedent basis, therefore the metes and bounds of the claim cannot be determined.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50 and 51 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating and protecting against cisplatin and taxol induced neuropathy and a neuropathy resulting from sciatic nerve crush, or viral induced neuropathy or hereditary amyotrophic lateral sclerosis, comprising the administration of sonic hedgehog polypeptide, does not reasonably provide enablement for the treatment, prevent, or protection for other neuropathies, nor for the treatment of any neuropathy comprising the administration of a ptc-therapeutic other than a polypeptide at least 80% identical to the N-terminal auto-proteolytic fragment of a sonic hedgehog polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The specification presents the results obtained in several experimental neuropathic models, wherein sonic hedgehog is exogenously administered. Sonic hedgehog administration appeared to be effective in several of the models, e.g. cisplatin and taxol induced neuropathy (page 24) and rat sciatic nerve crush injury (page 79). However, in the other cases, it is unclear if administration of sonic hedgehog has a measurable beneficial effect. In the example of the SOD deficient mice no significant differences were found after treatment of male mice (page 77, l0). Further, in the galactose model of neuropathy, it is unclear if any difference between the groups

is significant (Figure 23). Additionally, treatment of diabetic rats with sonic hedgehog does not appear to have been attempted. Thus, it is unclear based, on the teachings of the specification, which of the multitude of neuropathic disorders contemplated are amenable to treatment with sonic hedgehog or any other ptc therapeutic. Subsequent to the filing of the instant Application, Oppenhiem *et al. Mol. Cell. Neuroscience* 13(348-361)1999 reported mixed results with the administration of sonic hedgehog in the treatment of a variety of different neuronal populations. Oppenhiem *et al.* report that the administration of exogenous sonic hedgehog to embryos *in vivo* or to motor neuron cultures failed to promote the survival of several different neuronal population including spinal motor neurons, spinal interneurons, sympathetic preganglionic neurons, sensory neurons and neuronal precursors (see the Abstract). Further, Oppenhiem *et al.* were "surprised to discover that Shh failed to promote the survival of chick embryo spinal chord cells and actually induced the death of apparent neuronal and floor-plate cells during the first stage of spinal chord programmed cell death" (see page 353, col. 2). Thus, it is unclear which types of neuropathies are amendable to treatment. The specification has merely provided to the skilled artisan an invitation to begin further research and investigation into which other of the multitude of pathologies involving the motor and/or sensory nervous systems could ultimately be treated as claimed; and then to begin further research and investigation into the particular methodologies of administration and treatment schedule that would be required once and amendable disorder has been identified. The specification has provided no guiding principle to identify which particular neuropathies would be amendable to treatment, and nor is such a

principle known in the art. The skilled artisan is therefore left to undergo extensive random trial and error experimentation in order to determine which neuropathologies are amendable to treatment.

Additionally, the specification has provide results with the administration of the N-terminal auto-proteolytic fragment of a sonic hedgehog polypeptide, PEGylated or as a fusion with an immunoglobin (pg 79) yet the claims encompass the administration of any compound that is encompassed by the definition of a hedgehog or ptc-therapeutic, i.e., any compound that "binds to patched and alters its signal transduction activity , or compounds which alter the binding and/or activity of a protein (e.g., intracellular) involved in patched signal pathway, and compounds which alter the level of expression of a hedgehog protein, a patched protein or a protein involved in the intracellular signal transduction pathway of patched" (see page 47, lines 23-28 and claims 30 and 31). The specification puts forth that PKA inhibitors are ptc-therapeutics (page 35), yet the specification does not teach that PKA inhibitors are effective in the treatment of any particular peripheral neuropathic disorders. Further, as put forth above, it is well appreciated that the activities of patched are extremely complex and as yet controversial and incompletely identified (see *Stull and Iacovitti, Experimental Neurobiology* 169(1)36-43, 2001, especially page 40); the claims, therefore, encompass treatments involving the administration of compounds which alter any aspect of patched signaling. However, there appears to be no disclosure of such molecules, nor guidance as to how to produce such a molecule, nor is such a molecule known in the art. The claims claim a process using such a molecule, yet the

specification appears to offer no guidance other than an invitation to the skilled artisan to perform random trial and error experimentation to try to find such a molecule (see page 48-49 for example), if such a molecule can be found. Further, the art is equivocal about the role of patched signaling pathways in the development and/or maintenance of neural tissue. The results of *Stull and Iacovitti, Experimental Neurobiology* 169(1)36-43, 2001 suggest that sonic hedgehog does not signal through either PKA, IP-3K/PKC or DA signal transduction pathways (see page 40 first paragraph) and that activation of PKA does not inhibit sonic hedgehog induction neurons (see page 40, 2nd col. 1st paragraph). Further, the effects of hedgehog polypeptides on motor and sensory neurons are unpredictable and sometimes contrary to what would be needed for a therapy, e.g. *Oppenheim et al*, discovered that sonic hedgehog can actually induce neuron cell death, and that altered concentrations of sonic hedgehog induce aberrant phenotypes that are removed by programmed cell death (see the Abstract) - thus adding to the complexity and uncertainty involved in the use of sonic hedgehog on neural tissues.

Therefore, due to the lack of direction/guidance presented in the specification regarding which structural features are required of a ptc-therapeutic in order to provide activity, the absence of working examples directed to same, the complex nature of the effect of sonic hedgehog on motor and sensory nerves, the contradictory state of the prior art (see *Stull and Iacovitti* and *Oppenheim et al* above), the breadth of the claims which encompass a multitude of distinct and disparate neuropathies, the breadth of the claims which encompass a multitude of undisclosed ptc-therapeutics, and the state of the prior art which does not appear to embrace a ptc-therapeutic

useful for the treatment of peripheral neuropathies other than a polypeptide hedgehog ptc-therapeutic, undue experimentation would be required of the skilled artisan to make the claimed invention.

11. Claims 1-8, 10, 11, 13, 14, 16-23, 30, 31, 41, 44, 45-47, 48, 50 and 51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims require *in vivo* methods of preventing dysfunction and/or degradation of functional performance of motor or sensory nerves comprising administering a "therapeutic amount" or an "effect amount" of a "ptc therapeutic" or a "therapeutically effective amount" of a "ptc therapeutic", or a "protective amount", comprising the administration of a ptc therapeutic (e.g. small molecule agonist/antagonist or a protein that is "homologous" to a hedgehog protein) such molecule or protein being one that alters the activity of a patched signaling pathway, as defined in the specification as a "ptc therapeutic" at pages 11 and 48. However, there appears to be no description of such a molecule, nor guidance as to what structural characteristics such a molecule might possess, nor is such a molecule known in the art, nor has the specification put forth what structural characteristics a protein that is homologous to a hedgehog protein is required to have in order to function within the definition of "ptc-therapeutic".

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-4, 6-11, 13-18, 21, 30, 31, 41, 44-48, and 50, 51 rejected under 35 U.S.C. 102(b) as being anticipated by WO 95/18856, Ingham et al., 13 July 1995.

Ingham et al., disclose that administration of sonic hedgehog can be used to treat conditions affecting the peripheral nervous system (pg 56, Line 27) e.g. viral or cisplatin induced neuropathy (pg 57, L24) or hereditary neuropathies such as amyotrophic lateral sclerosis (pg 56, L35), the severity of ALS being associated with age . Further, Ingham et al., disclose that the sonic hedgehog can be obtained from expression in mammalian or baculovirus expression systems (pg 111), both of which would necessarily result in a lipophilic modification of the protein with an aromatic, e.g. cholesterol modification and a fatty acid modification, e.g. palmitic acid (C_{16} alkyl). Further, the protein can be a fusion protein, e.g.c-myc (pg 112). Such treatments can be provided prophylactically (e.g pge 57). Additionally, the sonic hedgehog protein used in the method taught be Ingham et al. would necessarily mimic hedgehog mediated signal transduction (e.g. claims 30 and 31), absent evidence to the contrary.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-4, 6-11,13-18, 21, 30, 31, 41, 44-48, 50, 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/18856, Ingham et al., 13 July 1995, as applied to claim 1-4, 6-11, 13-18, 21, 30, 31, 41, 44-48, and 50, 51 above, and in view of Porter JA *et al., Science* 274(255-259)1996. As set forth above, Ingham et al., disclose methods of treating peripheral neuropathies comprising the administration of sonic hedgehog polypeptides, however, Ingham et al., do not mention that the hedgehog polypeptide be modified with a lipophilic moiety. As set forth above, Ingham et al., disclose that the hedgehog polypeptides can be obtained from expression in mammalian or baculovirus expression systems (pg 111), both of which would necessarily result in a lipophilic modification of the protein with an aromatic, e.g. cholesterol modification and a fatty acid modification, e.g. palmitic acid (C_{12} alkyl).

Although the claims, in their current form, do not require that the sonic hedgehog polypeptides be isolated on the basis of a lipophilic moiety, the claims encompass such methods. Porter JA *et al.* disclose that mammalian hedgehog proteins derived from eukaryotic expression systems are conjugated to a cholesterol moiety, and suggest that this cholesterol modification is required for normal development in animals (see the Abstract). Therefore, it would have been

obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation of success to use cholesterol modified hedgehog protein as taught by Porter JA *et al.* when treating peripheral neuropathies as taught by Ingham et al. The motivation to do so was provided by Porter JA et al., who stated that the lack of cholesterol modification of hedgehog may account for some of the undesirable effects of perturbed cholesterol biosynthesis on animal development (see the discussion).

Claims 1-4, 6-11,13-21, 23, 30, 31, 41, 44-48, 50, 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/18856, Ingham et al., 13 July 1995, as applied to claim 1-4, 6-11,13-18, 21, 30, 31, 41, 44-48, 50, 51 above, and in view of Pepinsky RB *et al.*, *J. Biol. Chem.* 273(22)14037-14045, 1996. As set forth above, Ingham et al., disclose methods of treating peripheral neuropathies comprising the administration of sonic hedgehog polypeptides, however, Ingham et al., do not mention that the hedgehog polypeptide be modified with a lipophilic moiety. As set forth above, Ingham et al., disclose that the hedgehog polypeptides can be obtained from expression in mammalian or baculovirus expression systems (pg 111), both of which would necessarily result in a lipophilic modification of the protein with an aromatic, e.g. cholesterol modification and a fatty acid modification, e.g. palmitic acid (C_{16} alkyl).

Although the claims, in their current form, do not require that the sonic hedgehog polypeptides be isolated on the basis of a lipophilic moiety, the claims encompass such methods. Pepinsky RB *et al.* disclose that sonic hedgehog expressed in eukaryotes is modified with a

cholesterol moiety at the C-terminus and with a palmitic acid moiety at the N-terminus (see the Abstract). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation of success to use palmitoyl modified hedgehog protein as taught by Pepinsky RB *et al.* when treating peripheral neuropathies as taught by Ingham et al. The motivation to do so was provided by Pepinsky RB *et al.* who stated that palmitoylation of hedgehog increased the potency of hedgehog by about 30 percent (see the Abstract).

16. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/18856, Ingham et al., 13 July 1995, as applied to claim 1-4, 6-11, 13-18, 21, 30, 31, 41, 44-48, and 50, 51 above, and in view off WO 96/29342, Jonassen et al., 26 Sep. 1996. As set forth above, Ingham et al., disclose methods of treating peripheral neuropathies comprising the administration of sonic hedgehog polypeptides, however, Ingham et al., do not mention that the hedgehog polypeptide be modified with a lipophilic moiety, e.g. derivatives such as phenanthrene, anthracene, naphthalene and naphthacene. Jonassen *et al.* teach the lipophilic moieties such as phenanthrene derivatives (e.g. page 4) are useful for modifying peptide hormones because such modifications protract the action of the peptides (see the Abstract for example). Further, Jonassen et al. teach that the particular derivative to use is a matter of routine optimization, depending on the particular disease to be treated (page 7). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to modify the sonic hedgehog

peptide with phenanthrene or a derivative as suggested by Jonassen et al. when practicing the treatment methods of Ingham et al.. The motivation to do so was provided by Jonassen et al. who teach that lipophilic modification of peptide protracts the action of the modified peptides (see the Abstract).

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

August 10, 2001

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600